Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original) A method of synthesizing an insulin polypeptide-oligomer conjugate comprising:

contacting a proinsulin polypeptide comprising an insulin polypeptide coupled to one or more peptides by peptide bond(s) capable of being cleaved to yield the insulin polypeptide with an oligomer comprising a hydrophilic moiety and a lipophilic moiety under conditions sufficient to couple the oligomer to the insulin polypeptide portion of the proinsulin polypeptide and provide a proinsulin polypeptide-oligomer conjugate; and

cleaving the one or more peptides from the proinsulin polypeptide-oligomer conjugate to provide the insulin polypeptide-oligomer conjugate.

2. (Original) The method according to Claim 1, wherein the contacting of the proinsulin polypeptide with the oligomer comprises:

contacting the oligomer with an activating agent under conditions sufficient to provide an activated oligomer capable of coupling to a nucleophilic functionality on the proinsulin polypeptide; and

contacting the activated oligomer with the proinsulin polypeptide under conditions sufficient to provide the proinsulin polypeptide-oligomer conjugate.

3. (Original) The method according to Claim 2, wherein the contacting of the oligomer with the activating agent and the contacting of the activated oligomer with the proinsulin polypeptide is performed in situ.

4. (Original) The method according to Claim 2, wherein the molar ratio of activated oligomer to proinsulin polypeptide is greater than about 1:1.

5. (Original) The method according to Claim 2, wherein the molar ratio of activated oligomer to proinsulin polypeptide is greater than about 3:1.

6. (Original) The method according to Claim 2, wherein the molar ratio of activated oligomer to proinsulin polypeptide is greater than about 4:1.

7. (Original) The method according to Claim 6, wherein the yield of insulin polypeptide-oligomer conjugate is greater than 75 percent.

8. (Original) The method according to Claim 6, wherein the yield of insulin polypeptide-oligomer conjugate is greater than 80 percent.

9. (Original) The method according to Claim 6, wherein the yield of insulin polypeptide-oligomer conjugate is greater than 85 percent.

10. (Original) The method according to Claim 6, wherein the yield of insulin polypeptide-oligomer conjugate is greater than about 90 percent.

11. (Original) The method according to Claim 1, wherein the yield of insulin polypeptide-oligomer conjugate is greater than 75 percent.

12. (Original) The method according to Claim 1, wherein the yield of insulin polypeptide-oligomer conjugate is greater than 80 percent.

13. (Original) The method according to Claim 1, wherein the yield of insulin polypeptide-oligomer conjugate is greater than 85 percent.

14. (Original) The method according to Claim 1, wherein the yield of insulin polypeptide-oligomer conjugate is greater than about 90 percent.

15. (Original) The method according to Claim 1, wherein the yield of insulin polypeptide-oligomer conjugate is greater than about 95 percent.

16. (Original) The method according to Claim 1, wherein the insulin polypeptide has an A-chain polypeptide and a B-chain polypeptide, and wherein the one or more peptides comprise a

connecting peptide coupled at a first end to the C-terminus of the B-chain polypeptide and coupled at a second end to the N-terminus of the A-chain polypeptide.

17. (Original) The method according to Claim 16, wherein the connecting peptide is a C-peptide polypeptide.

18. (Original) The method according to Claim 16, wherein the connecting peptide is C-peptide.

19. (Original) The method according to Claim 16, wherein the connecting peptide is devoid of lysine residues.

20. (Original) The method according to Claim 16, wherein the one or more peptides further comprise a leader peptide coupled to the N-terminus of the B-chain polypeptide.

21. (Original) The method according to Claim 20, wherein the leader peptide is devoid of lysine residues.

22. (Original) The method according to Claim 1, wherein the insulin polypeptide has an A-chain polypeptide and a B-chain polypeptide, and wherein the one or more peptides is a connecting peptide coupled at a first end to the C-terminus of the B-chain polypeptide and at a second end to the N-terminus of the A-chain polypeptide.

23. (Original) The method according to Claim 1, wherein the insulin polypeptide has an A-chain polypeptide and a B-chain polypeptide, and wherein the one or more peptides is a connecting peptide coupled at a first end to the C-terminus of the B-chain polypeptide and at a second end to the N-terminus of the A-chain polypeptide, and a leader peptide coupled to the N-terminus of the B-chain polypeptide.

24. (Original) The method according to Claim 1, wherein the proinsulin polypeptide is proinsulin.

25. (Original) The method according to Claim 1, wherein the proinsulin polypeptide is proinsulin coupled at the N-terminus of the B-chain to a leader peptide by a peptide bond that is cleavable .

26. (Original) The method according to Claim 1, wherein the insulin polypeptide is insulin.

27. (Original) The method according to Claim 26, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

28. (Original) The method according to Claim 1, wherein the insulin polypeptide is an insulin analog selected from the group consisting of GlyA21 insulin, human; GlyA21 GlnB3 insulin, human; AlaA21 insulin, human; AlaA21 GlnB3 insulin, human; GlnB3 insulin, human; GlnB30 insulin, human; GlyA21 GluB30 insulin, human; GlyA21 GlnB3 GluB30 insulin, human; GlnB3 GluB30 insulin, human; AspB28 insulin, human; LysB28 insulin, human; LeuB28 insulin, human; ValB28 insulin, human; AlaB28 insulin, human; AspB28 ProB29 insulin, human; LysB28 ProB29 insulin, human; LeuB28 ProB29 insulin, human; ValB28 ProB29 insulin, human; AlaB28 ProB29 insulin, human.

29. (Original) The method according to Claim 1, wherein the insulin polypeptide-oligomer conjugate is amphiphilically balanced.

30. (Original) The method according to Claim 1, wherein the oligomer is present as a substantially monodispersed mixture.

31. (Original) The method according to Claim 1, wherein the oligomer is present as a monodispersed mixture.

32. (Original) The method according to Claim 1, wherein the hydrophilic moiety is a polyalkylene glycol moiety.

33. (Original) The method according to Claim 32, wherein the polyalkylene glycol moiety is a polyethylene glycol moiety.

34. (Original) The method according to Claim 32, wherein the polyalkylene glycol moiety has between 1 and 50 polyalkylene glycol subunits.

35. (Original) The method according to Claim 32, wherein the polyalkylene glycol moiety has between 3 and 50 polyalkylene glycol subunits.

36. (Original) The method according to Claim 32, wherein the polyalkylene glycol moiety has between 2 and 10 polyalkylene glycol subunits.

37. (Original) The method according to Claim 32, wherein the polyalkylene glycol moiety has between 4 and 10 polyalkylene glycol subunits.

38. (Original) The method according to Claim 32, wherein the polyalkylene glycol moiety has at least 2 polyalkylene glycol subunits.

39. (Original) The method according to Claim 1, wherein the lipophilic moiety is an alkyl or fatty acid moiety.

40. (Original) The method according to Claim 1, wherein the lipophilic moiety has between 1 and 28 carbon atoms.

41. (Original) The method according to Claim 1, wherein the lipophilic moiety has between 2 and 24 carbon atoms.

42. (Original) The method according to Claim 1, wherein the lipophilic moiety has between 3 and 18 carbon atoms.

43. (Original) The method according to Claim 1, wherein the lipophilic moiety has between 4 and 12 carbon atoms.

44. (Original) The method according to Claim 1, wherein the lipophilic moiety has between 5 and 7 carbon atoms.

45. (Original) The method according to Claim 1, wherein the lipophilic moiety has between 4 and 14 carbon atoms.

46. (Original) The method according to Claim 1, wherein the cleaving of the one or more peptides from the proinsulin polypeptide-oligomer conjugate comprises contacting the proinsulin polypeptide-oligomer conjugate with one or more enzymes that are capable of cleaving the bond(s) between the one or more peptides and the insulin polypeptide under conditions sufficient to cleave the one or more peptides from the proinsulin polypeptide-oligomer conjugate.

47. (Original) The method according to Claim 46, wherein the one or more enzymes are selected from the group consisting of trypsin, carboxy peptidase B, and mixtures thereof.

48. (Original) The method according to Claim 16, wherein the connecting peptide has a terminal amino acid residue at the first end, and wherein the cleaving of the connecting peptide from the proinsulin polypeptide-oligomer conjugate comprises:

contacting the proinsulin polypeptide-oligomer conjugate with a first enzyme under conditions sufficient to provide a terminal amino acid residue-insulin polypeptide-oligomer conjugate; and

contacting the terminal amino acid residue-insulin polypeptide-oligomer conjugate with a second enzyme under conditions sufficient to provide the insulin polypeptide-oligomer conjugate.

49. (Original) The method according to Claim 48, wherein the terminal amino acid residue is an arginine residue.

50. (Original) The method according to Claim 49, wherein the insulin polypeptide is insulin, and wherein the connecting peptide is human C-peptide.

51. (Original) The method according to Claim 48, wherein the contacting of the proinsulin polypeptide-oligomer conjugate with a first enzyme and the contacting of the terminal amino acid residue-insulin polypeptide-oligomer conjugate with a second enzyme occur substantially concurrently.

52. (Original) The method according to Claim 51, wherein the first enzyme and the second enzyme are provided in a mixture comprising the first enzyme and the second enzyme.

53. (Original) The method according to Claim 48, wherein the first enzyme is trypsin, and wherein the second enzyme is carboxy peptidase B.

Claims 54-247 are withdrawn.

248. (Original) A method of synthesizing an insulin polypeptide-acyl oligomer conjugate comprising enzymatically cleaving one or more peptides from a proinsulin polypeptide-acyl oligomer conjugate to provide the insulin polypeptide-acyl oligomer conjugate.

249. (Original) The method according to Claim 248, wherein the insulin polypeptide has an A-chain polypeptide and a B-chain polypeptide, and wherein the one or more peptides comprise a connecting peptide coupled at a first end to the C-terminus of the B-chain polypeptide and coupled at a second end to the N-terminus of the A-chain polypeptide.

250. (Original) The method according to Claim 249, wherein the connecting peptide is a C-peptide polypeptide.

251. (Original) The method according to Claim 249, wherein the connecting peptide is C-peptide.

252. (Original) The method according to Claim 249, wherein the connecting peptide is devoid of lysine residues.

253. (Original) The method according to Claim 249, wherein the one or more peptides further comprise a leader peptide coupled to the N-terminus of the B-chain polypeptide.

254. (Original) The method according to Claim 249, wherein the leader peptide is devoid of lysine residues.

255. (Original) The method according to Claim 248, wherein the proinsulin polypeptide is proinsulin.

256. (Original) The method according to Claim 248, wherein the proinsulin polypeptide is proinsulin coupled at its N-terminus to a leader peptide by a peptide bond that is cleavable.

257. (Original) The method according to Claim 248, wherein the insulin polypeptide is insulin.

258. (Original) The method according to Claim 257, wherein the acyl oligomer is coupled to the lysine at the B29 position of the insulin.

259. (Original) The method according to Claim 248, wherein the insulin polypeptide-acyl oligomer conjugate is amphiphilically balanced.

260. (Original) The method according to Claim 248, wherein the acyl oligomer portion of the insulin polypeptide-acyl oligomer conjugate comprises a hydrophilic moiety and a lipophilic moiety.

261. (Original) The method according to Claim 260, wherein the hydrophilic moiety is a polyethylene glycol moiety.

262. (Original) The method according to Claim 261, wherein the polyethylene glycol moiety has between 1 and 50 polyethylene glycol subunits.

263. (Original) The method according to Claim 261, wherein the polyethylene glycol moiety has between 3 and 50 polyethylene glycol subunits.

264. (Original) The method according to Claim 261, wherein the polyethylene glycol moiety has between 2 and 10 polyethylene glycol subunits.

265. (Original) The method according to Claim 261, wherein the polyethylene glycol moiety has between 4 and 10 polyethylene glycol subunits.

266. (Original) The method according to Claim 261, wherein the polyethylene glycol moiety has at least 2 polyethylene glycol subunits.

267. (Original) The method according to Claim 260, wherein the lipophilic moiety is an alkyl or a fatty acid moiety.

268. (Original) The method according to Claim 267, wherein the lipophilic moiety has between 1 and 28 carbon atoms.

269. (Original) The method according to Claim 267, wherein the lipophilic moiety has between 2 and 24 carbon atoms.

270. (Original) The method according to Claim 267, wherein the lipophilic moiety has between 3 and 18 carbon atoms.

271. (Original) The method according to Claim 267, wherein the lipophilic moiety has between 4 and 12 carbon atoms.

272. (Original) The method according to Claim 267, wherein the lipophilic moiety has between 5 and 7 carbon atoms.

273. (Original) The method according to Claim 267, wherein the lipophilic moiety has between 4 and 14 carbon atoms.

274. (Original) The method according to Claim 248, wherein the enzymatically cleaving of the one or more peptides from the proinsulin polypeptide-acyl oligomer conjugate comprises contacting the proinsulin polypeptide-oligomer conjugate with one or more enzymes that are capable of cleaving the bond(s) between the one or more peptides and the insulin polypeptide under conditions sufficient to cleave the one or more peptides from the proinsulin polypeptide-oligomer conjugate.

275. (Original) The method according to Claim 274, wherein the one or more enzymes are selected from the group consisting of trypsin, carboxy peptidase B, and mixtures thereof.

276. (Original) The method according to Claim 249, wherein the connecting peptide has a terminal amino acid residue at the first end, and wherein the enzymatically cleaving of the connecting peptide from the proinsulin-acyl oligomer conjugate comprises:

contacting the proinsulin polypeptide-acyl oligomer conjugate with a first enzyme under conditions sufficient to provide a terminal amino acid residue-insulin polypeptide-oligomer conjugate; and

contacting the terminal amino acid residue-insulin polypeptide-acyl oligomer conjugate with a second enzyme under conditions sufficient to provide the insulin-acyl oligomer conjugate.

277. (Original) The method according to Claim 276, wherein the terminal amino acid residue is an arginine residue.

278. (Original) The method according to Claim 277, wherein the insulin polypeptide is insulin, and wherein the connecting peptide is C-human peptide.

279. (Original) The method according to Claim 276, wherein the contacting of the proinsulin-oligomer conjugate with a first enzyme and the contacting of the terminal amino acid residue-insulin polypeptide-acyl oligomer conjugate with a second enzyme occur substantially concurrently.

280. (Original) The method according to Claim 276, wherein the first enzyme and the second enzyme are provided in a mixture comprising the first enzyme and the second enzyme.

281. (Original) The method according to Claim 276, wherein the first enzyme is trypsin, and wherein the second enzyme is carboxy peptidase B.

Claims 282-370 are withdrawn.

371. (Original) A method of synthesizing a proinsulin polypeptide-oligomer conjugate comprising contacting a proinsulin polypeptide with an oligomer comprising a hydrophilic moiety and a lipophilic moiety under conditions sufficient to provide the proinsulin polypeptide-oligomer conjugate.

372. (Original) The method according to Claim 371, wherein the proinsulin polypeptide comprises an insulin polypeptide having an A-chain polypeptide, a B-chain polypeptide, and a connecting peptide coupled at a first end to the C-terminus of the B-chain polypeptide and coupled at a second end to the N-terminus of the A-chain polypeptide.

373. (Original) The method according to Claim 372, wherein the connecting peptide is a C-peptide polypeptide.

374. (Original) The method according to Claim 372, wherein the connecting peptide is C-peptide.

375. (Original) The method according to Claim 372, wherein the connecting peptide is devoid of lysine residues.

376. (Original) The method according to Claim 372, wherein the proinsulin polypeptide further comprises a leader peptide coupled to the N-terminus of the B-chain polypeptide.

377. (Original) The method according to Claim 376, wherein the leader peptide is devoid of lysine residues.

378. (Original) The method according to Claim 371, wherein the proinsulin polypeptide comprises an insulin polypeptide having an A-chain polypeptide and a B-chain polypeptide, a connecting peptide coupled at a first end to the C-terminus of the B-chain polypeptide and at a second end to the N-terminus of the A-chain polypeptide, and a leader peptide coupled to the N-terminus of the B-chain polypeptide.

379. (Original) The method according to Claim 378, wherein the insulin polypeptide is insulin.

380. (Original) The method according to Claim 379, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

381. (Original) The method according to Claim 371, wherein the proinsulin polypeptide is proinsulin.

382. (Original) The method according to Claim 371, wherein the insulin polypeptide-oligomer conjugate is amphiphilically balanced.

383. (Original) The method according to Claim 371, wherein the oligomer is present as a substantially monodispersed mixture.

384. (Original) The method according to Claim 371, wherein the oligomer is present as a monodispersed mixture.

385. (Original) The method according to Claim 371, wherein the hydrophilic moiety is a polyalkylene glycol moiety.

386. (Original) The method according to Claim 385, wherein the polyalkylene glycol moiety is a polyethylene glycol moiety.

387. (Original) The method according to Claim 385, wherein the polyalkylene glycol moiety has between 1 and 50 polyalkylene glycol subunits.

388. (Original) The method according to Claim 385, wherein the polyalkylene glycol moiety has between 3 and 50 polyalkylene glycol subunits.

389. (Original) The method according to Claim 385, wherein the polyalkylene glycol moiety has between 2 and 10 polyalkylene glycol subunits.

390. (Original) The method according to Claim 385, wherein the polyalkylene glycol moiety has between 4 and 10 polyalkylene glycol subunits.

391. (Original) The method according to Claim 385, wherein the polyalkylene glycol moiety has at least 2 polyalkylene glycol subunits.

392. (Original) The method according to Claim 371, wherein the lipophilic moiety is an alkyl or fatty acid moiety.

393. The method according to Claim 371, wherein the lipophilic moiety has between 1 and 28 carbon atoms.

394. (Original) The method according to Claim 371, wherein the lipophilic moiety has between 2 and 24 carbon atoms.

395. (Original) The method according to Claim 371, wherein the lipophilic moiety has between 3 and 18 carbon atoms.

396. (Original) The method according to Claim 371, wherein the lipophilic moiety has between 4 and 12 carbon atoms.

397. (Original) The method according to Claim 371, wherein the lipophilic moiety has between 5 and 7 carbon atoms.

398. (Original) The method according to Claim 371, wherein the lipophilic moiety has between 4 and 14 carbon atoms.

Claims 399-445 are withdrawn.

Claims 446-458 are cancelled.

Claims 459-467 are withdrawn.